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Adding Fluorine Helps Ailing Antibiotic

Tests in cell cultures show that a single fluorine helps neomycin outwit drug-resistant bacteria

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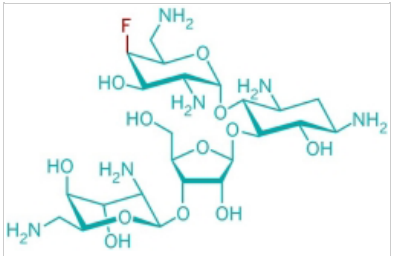

Fluorinated neomycin analog

A strategically placed fluorine today could keep antibiotic resistance at bay. Aminoglycosides are a class of antibiotics that have traditionally been useful against infections in patients with severe burns or cystic fibrosis. Antibiotic-resistant bacteria have emerged, however, carrying an arsenal of aminoglycoside-inactivating enzymes. One approach to counter the enzymes has been to remove certain aminoglycoside hydroxyl groups. But that change can make the drugs toxic to the kidneys. **Stephen Hanessian** and colleagues at the University of Montreal instead tinkered with neomycin B, an aminoglycoside and the active ingredient in popular over-the-counter antibiotic ointments, to see whether fluorination might help. When Hanessian's team replaced the 4´-hydroxyl group on neomycin's A-ring with an axial fluorine (shown), they created an analog that evades aminoglycoside-inactivating enzymes in bacterial cell cultures (*Chem. Sci.* 2014, DOI: **10.1039/c4sc01626b**). Adding an (*S*)-hydroxyaminobutyric acid to neomycin's B-ring and fluorinating it was also effective (*ACS Chem. Biol.* 2014, DOI: **10.1021/cb5003416**). To see how fluorine made a difference, Hanessian's team used X-ray crystallography. Aminoglycosides interfere with bacterial protein synthesis by binding tightly to a microbe's ribosomal RNA in a position called the A-site. The crystal structure shows that axial fluorine contacts a guanine nucleic acid in the A-site.

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